Correlation of Plasma 25-Hydroxyvitamin D Levels With Severity of Primary Hyperparathyroidism and Likelihood of Parathyroid Adenoma Localization on Sestamibi Scan

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Objectives: To determine the relationship between preoperative plasma 25-hydroxyvitamin D (25(OH)D) levels and severity of primary hyperparathyroidism (PHPT) and to explore whether presurgical 25(OH)D levels could predict the likelihood of positive results on technetium Tc 99m sestamibi scintigraphy.

Design: Retrospective analysis.

Setting: Tertiary university referral center.

Patients: A total of 421 consecutive patients underwent preoperative sestamibi scintigraphy and parathyroid exploration. Patients with cholecalciferol (vitamin D) deficiency, defined as plasma levels lower than 25 ng/mL, were compared with patients having no vitamin D deficiency. We explored the relationship between 25(OH)D levels and intact parathyroid hormone (iPTH) levels, alkaline phosphatase (ALKP) levels, adenoma weight, binary sestamibi scan results, and postoperative serum calcium levels (at 1 week and 6 months).

Main Outcome Measures: We hypothesized that severity of hypovitaminosis D would correlate with severity of PHPT and predict the likelihood of a positive finding on sestamibi scan.

Results: Concentrations of iPTH and ALKP and parathyroid adenoma weight were significantly higher in patients with lower 25(OH)D levels (P < .01 for all). Patients with hypovitaminosis D had a greater percentage decrease in serum calcium levels 1 week and 6 months postoperatively (P < .05). Median 25(OH)D levels were lower in patients with positive sestamibi scan results (P < .001).

Conclusions: Patients with hypovitaminosis D present with more advanced indices of PHPT. Parathyroid sestamibi scanning is more likely to show positive results for this subset of patients who may then benefit from sestamibi scan–directed surgical intervention.

evaluate the relationship between plasma 25(OH)D concentrations and the severity of PHPT.

METHODS

After obtaining approval from the Johns Hopkins institutional review board, we compiled a database of patients who underwent parathyroid surgery from July 2002 to August 2006. A total of 421 consecutive patients who underwent preoperative sestamibi scintigraphy and parathyroid exploration for PHPT with resection of at least 1 enlarged parathyroid gland were included in this study. Patients with multiple endocrine neoplasia and/or secondary and/or tertiary hyperparathyroidism were excluded in this study. Patients with multigland disease, the weight of the heaviest gland was used for the statistical analysis.

Data reviewed included age, sex, and preoperative laboratory values, including serum calcium (normal range, 8.4-10.5 mg/dL), alkaline phosphatase (ALKP) (normal range, 30-120 U/L), intact parathyroid hormone (iPTH) (normal range, 10-65 pg/mL), and 25(OH)D levels. Adenoma weight, operative notes, pathology reports, and sestamibi scan results were all reviewed. To convert calcium to millimoles per liter, multiply by 0.25; to convert alkaline phosphatase to microkatals per liter, multiply by 0.0167; to convert intact parathyroid hormone (iPTH) (normal range, 10-65 pg/mL), alkaline phosphatase (ALKP) (normal range, 30-120 U/L), intact parathyroid hormone (iPTH) (normal range, 10-65 pg/mL), and 25(OH)D levels. Adenoma weight, operative notes, pathology reports, and sestamibi scan results were all reviewed. To convert calcium to millimoles per liter, multiply by 0.25; to convert ALKP to microkatals per liter, multiply by 0.0167; to convert calcium to millimoles per liter, multiply by 0.25; to convert alkaline phosphatase to microkatals per liter, multiply by 0.0167; to convert calcium to millimoles per liter, multiply by 0.25; to convert iPTH to nanograms per liter, multiply by 0.1053.

SESTAMIBI SCANS

All patients underwent an outpatient parathyroid sestamibi scan followed by parathyroid exploration for PHPT. Sestamibi scan reports were reviewed. Confidence for identifying a parathyroid adenoma was assessed semiquantitatively using a 2-point scale: 0 indicated a negative or indeterminate scan finding; and 1 indicated a finding positive for adenoma.

Table 1. Demographic and Clinical Characteristics of 421 Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61 (23 to 95)</td>
</tr>
<tr>
<td>Men</td>
<td>114 (27.1)</td>
</tr>
<tr>
<td>Adenoma weight, mg</td>
<td>565 (30 to 10 780)</td>
</tr>
<tr>
<td>25(OH)D, ng/dL</td>
<td>21 (4 to 73)</td>
</tr>
<tr>
<td>ALKP, U/L</td>
<td>92 (28 to 292)</td>
</tr>
<tr>
<td>iPTH, PreOp, pg/mL</td>
<td>11.1 (7.7 to 14.6)</td>
</tr>
<tr>
<td>Calcium, 1-wk PostOp, mg/dL</td>
<td>121 (3 to 854)</td>
</tr>
<tr>
<td>Calcium, 6-mo PostOp, mg/dL</td>
<td>9.6 (7.0 to 11.8)</td>
</tr>
<tr>
<td>Calcium, 6-mo PostOp, %</td>
<td>14.3 (−5.7 to 38.0)</td>
</tr>
<tr>
<td>iPTH, 1-wk PostOp, pg/mL</td>
<td>9.5 (8.3 to 10.8)</td>
</tr>
<tr>
<td>iPTH, 1-wk PostOp, %</td>
<td>14.2 (−5.0 to 32.4)</td>
</tr>
<tr>
<td>iPTH, 6-mo PostOp, %</td>
<td>66.9 (−66.7 to 98.5)</td>
</tr>
<tr>
<td>iPTH, 6-mo PostOp, %</td>
<td>61.1 (−75.8 to 96.5)</td>
</tr>
<tr>
<td>Sestamibi scan findings</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>300 (71.3)</td>
</tr>
<tr>
<td>Suspicious or negative</td>
<td>121 (28.7)</td>
</tr>
</tbody>
</table>

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; iPTH, intact parathyroid hormone; PostOp, postoperative measurement; PreOp, preoperative measurement.

STATISTICAL ANALYSIS

Demographic and clinical characteristics were summarized using descriptive statistics. Categorical data were summarized with frequencies and percentages, and continuous data with medians and ranges because many of the measures were not normally distributed. Vitamin D deficiency was defined as a plasma level lower than 25 ng/mL, and patients with 25(OH)D deficiency were compared with patients with normal 25(OH)D levels using χ² tests for categorical data and Wilcoxon rank sum tests for continuous data. Linear regression analysis was used to assess the association of vitamin D levels with other preoperative and postoperative measures. Logistic regression analysis was used to test the statistical significance of the observed relationships between vitamin D deficiency and positive sestamibi scan results, after adjusting for age and sex. Analysis was performed using SAS version 9.1.3 software (SAS Institute, Cary, North Carolina). All reported P values are 2-sided, and P < .05 was considered significant.

RESULTS

We performed a retrospective analysis of 421 patients who underwent preoperative sestamibi scintigraphy and parathyroid exploration for PHPT. The demographic and clinical characteristics of the 421 patients are summarized in Table 1. A total of 83.5% of patients had a single enlarged gland removed, while 16.5% had more than 1 en-
larged gland removed. The extent of parathyroid exploration and gland removal was based on intraoperative iPTH level analysis.

A high prevalence of hypovitaminosis D was found among these patients (61.0%). The median plasma level of 25(OH)D for the entire study group was 21 ng/mL (range, 4-73 ng/mL). Consistent with the diagnosis of PHPT, serum calcium and iPTH levels were elevated. Characteristics of the patients by 25(OH)D group are summarized in Table 2. Median serum calcium, iPTH, and ALKP levels were significantly higher in the group with lower 25(OH)D plasma levels (Figure 1). A significant inverse correlation between serum 25(OH)D level and both iPTH level and serum ALKP activity was also observed (Figure 2).

Patients with lower 25(OH)D levels exhibited significantly higher adenoma weight (Table 2). Also, there was an inverse correlation between serum 25(OH)D level and resected gland weight (P < .001) (Figure 3). These results were also adjusted for age and sex and continued to show a statistically significant inverse correlation (P < .01).

Patients in the vitamin D deficiency group had lower serum calcium levels 6 months postoperatively. They also exhibited a significantly greater percentage drop in their calcium levels at 1 week and 6 months compared with their preoperative levels (P < .05 for both) (Figure 4).

We found a high prevalence of hypovitaminosis D among patients with PHPT seen at our institution. Patients with lower plasma levels of 25(OH)D (<25 ng/mL) presented with more advanced indices of PHPT and were...
more likely to have a positive finding on parathyroid sesta-
mibi scan.

Bone turnover may be increased in PHPT.\(^8\) Low vita-
mamin D status in patients with PHPT is associated not only
with higher plasma iPTH levels but also with higher ALKP
activity, reflecting the increased severity of the disease in
this group of patients. Median preoperative plasma cal-
cium levels were only slightly higher for patients with lower
vitamin D levels but did reach statistical significance.

Patients with PHPT and low vitamin D status tend to
have a higher adenoma weight. The cause of this asso-
ciation is uncertain but likely multifactorial. Earlier re-
ports confirmed that parathyroid tumor weight is a sig-
nificant determinant of disease severity, as reflected by
serum levels of iPTH, calcium, and ALKP.\(^{11,12}\)

A possible explanation for our findings of more se-
vere presentation of the disease is that with 25(OH)D de-
iciency, the PTH gene, which is abnormally active in
PHPT, might be less constrained due to the loss of the
regulatory influence of 25(OH)D. Rao et al\(^{13}\) have sug-
gested that chronic vitamin D deficiency may accelerate
parathyroid adenoma growth and thereby exacerbate bone
turnover and bone loss.

Rao et al\(^{13}\) have proposed that 25(OH)D insufficiency
can reach levels low enough to stimulate parathyroid hor-
mones production and cause substantial effects on bio-
chemical indices indicative of mild PHPT. Similar to our
data, Silverberg et al\(^{14}\) found mean (SD) 25(OH)D levels
to be 21 (11) ng/mL in 124 patients with PHPT, with 53%
of patients having 25(OH)D deficiency as defined as plasma
25(OH)D levels less than 25 ng/mL. These findings may
be partially explained by the typically 25(OH)D-deficient
American diet. Silverberg et al\(^{15}\) also observed that pa-
tients with plasma levels of 25(OH)D in the lower group
had higher plasma iPTH levels, higher plasma ALKP con-
centrations, and higher bone turnover. However, their re-
sults differed from ours in multiple aspects. In another study,
Silverberg et al\(^{16}\) described only 55 patients who under-
went parathyroidectomy for mild PHPT, and they found
no correlation between vitamin D status and parathyroid
gland weight, preoperative localization on sestamibi scan,
or the postoperative surgical outcome.

Our results are also relevant to the management of
PHPT. In a patient who is not undergoing surgery, lim-
iting dietary intake of vitamin D and calcium are often
advised in the hope of minimizing the risk of hypercal-
cemia. However, moderate restriction of vitamin D in-
take will not reduce plasma calcium levels but will lead

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**Figure 3.** Level of plasma 25-hydroxyvitamin D (25(OH)D) by adenoma
weight. A, Linear regression (1271.9900 – 14.7157 \times 25(OH)D). B, in the box plot, the boxes represent the interquartile range; the center line is the median; and the bars extend to the 5th and 95th percentiles. To convert 25(OH)D to nanomoles per liter, multiply by 2.496.

**Figure 4.** Effect of preoperative plasma levels of 25-hydroxyvitamin D (25(OH)D) on postoperative serum calcium levels and percentage change vs preoperative levels in patients with primary hyperparathyroidism. A and B, Measured 1 week after surgery. C and D, Measured 6 months after surgery. All boxes represent the interquartile range; the center line is the median; and the bars extend to the 5th and 95th percentiles. To convert 25(OH)D to nanomoles per liter, multiply by 2.496; to convert calcium to millimoles per
liter, multiply by 0.25.
Positive

as opposed to standard 4-gland exploration.

benefit from an attempt at directed surgical intervention. 14,15 At present in the United States, more of these patients are more likely to benefit from surgical intervention. 14,15 At present in the United States, more of these patients are more likely to benefit from surgical intervention. 14,15

Patients with lower basal plasma 25(OH)D levels were more likely to have positive findings on sestamibi scans. Parameters suggestive of more advanced disease. In addition, patients with hypovitaminosis D present with laboratory deficiencies common among patients with PHPT, and patients with PHPT present with a myriad of subclinical signs and symptoms, a condition often referred to in the literature as asymptomatic PHPT. Thereofore, if vitamin D deficiency becomes even more widespread in the United States, the phenotype of PHPT could change, with more symptomatic disease emerging again.

The present study has several shortcomings. First, we evaluated only the indices associated with PHPT and did not evaluate the symptoms associated with the disease. Also, we cannot determine whether the parathyroid disease caused the observed vitamin D deficiency or whether the vitamin D deficiency resulted in worsening of PHPT. Nevertheless, our findings are relevant to the management of PHPT.

In summary, our observations suggest that vitamin D deficiency is common among patients with PHPT, and patients with hypovitaminosis D present with laboratory indices suggestive of more advanced disease. In addition, patients with lower basal plasma 25(OH)D levels were more likely to have positive findings on sestamibi scans. Parathyroid sestamibi scanning may be more useful in this patient population by helping to identify those who would benefit from an attempt at directed surgical intervention as opposed to standard 4-gland exploration.